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Letter to the Editor

Single Major Locus Models for Bipolar Disorder Are Implausible

To the Editor:

Knowledge of the likely mode of inheritance of a disorder is useful for design of linkage studies, choice of mode of statistical analysis and estimation of power to detect disease genes. In their paper, "Bipolar Disorder: Evidence for a Major Locus," Spence et al. [1995] report complex segregation analyses of Bipolar Disorder in which the best fitting model was a single, dominant mendelian major locus. Although the authors provide cautionary statements, they conclude that their results "should be at least somewhat reassuring to those using linkage studies in the search for a major bipolar locus." In contrast, we have recently applied a novel method of analysis to recurrence risk data on Bipolar Disorder and found that one or more major loci are most unlikely to underlie transmission of Bipolar Disorder whereas oligogenic epistatic models are plausible [Craddock et al. 1995]. Our findings will certainly not reassure those using conventional lod score approaches in large, densely affected families in a search for a presumed major bipolar locus because, under plausible oligogenic models, linkage strategies using non-parametric methods of analysis in large samples of affected sib-pairs are more appropriate [Risch, 1994].

In view of the marked difference between our findings and those of Spence et al., we would like to point out two weaknesses of complex segregation analysis.

1) The best-fitting model in a segregation analysis is the best fitting *of the models tested*. If a plausible (or true) model is not tested, the analysis cannot show that it is a likely model. As Spence et al. point out, they were unable to test polygenic/multifactorial models. Thus, an entirely plausible alternative to single locus transmission was not tested.
2) Segregation analyses ignore an important piece of information about a disease—the probandwise MZ twin concordance. For narrowly defined Bipolar Disorder this concordance is in excess of 60% [Bertelsen et al., 1977; Torgersen et al., 1986]. In our analysis of recurrence risk data we found that major locus models *are* consistent with observed recurrence risks in first degree relatives of Bipolar probands which is in agreement with the findings of Spence et al. (who used only information about first degree relatives). However, major locus models could not explain observed recurrence risks in *both* first degree relatives *and* MZ co-twins, whereas oligogenic epistatic models could. We believe it is important to make use of all available data. Although segregation analyses do not take account of knowledge of MZ twin concordance this could be achieved by calculating likelihoods for each model conditional upon the observed MZ twin concordance. If this were done for Bipolar Disorder, undoubtedly the findings from segregation analysis would be similar to our own: namely that single major locus models are implausible.

We would also like to point out that genetic models including more complex mechanisms such as dynamic mutation, mitochondrial inheritance or genomic imprinting were not considered either in our analyses or those of Spence et al. and may play a role in the genetics of Bipolar Disorder. However, our analyses indicate clearly that conventional major locus models (either single gene or heterogeneity models) are implausible whereas epistatic oligogenic models are plausible and investigators should find this knowledge useful in optimizing study design.

REFERENCES

Bertelsen A, Harvald B, Hauge M (1977): A Danish twin study of manic-depressive illness. British Journal of Psychiatry 130:330–351.

Craddock N, Khodel V, Van Eerdewegh P, Reich T (1995): Mathematical limits of multilocus models: The genetic transmission of bipolar disorder. Am J Hum Genet 57:690–702.

Risch NJ (1994): Mapping genes for psychiatric disorders. In ES Gershon, CR Cloninger (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, Inc., pp 47–61.

Spence MA, Flodman PL, Sadovnik AD, Bailey-Wilson JE, Ameli H, Remick RA (1995): Bipolar Disorder: Evidence for a major locus. Am J Med Genet 60:370–376.

Torgersen S (1986): Genetic factors in moderately severe and mild affective disorders. Arch Gen Psych 43:222–226.

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